



ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA-HQ-OPP-2012-0131; FRL-9362-4]

Calcium Gluconate; Exemption from the Requirement of a Tolerance

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This regulation establishes an exemption from the requirement of a tolerance for residues of calcium gluconate when used as an inert ingredient (sequestrant) in pesticide formulations applied to growing crops. ISK Biosciences Corporation submitted a petition to EPA under the Federal Food, Drug, and Cosmetic Act (FFDCA), requesting establishment of an exemption from the requirement of a tolerance. This regulation eliminates the need to establish a maximum permissible level for residues of calcium gluconate.

DATES: This regulation is effective [*insert date of publication in the Federal Register*]. Objections and requests for hearings must be received on or before [*insert date 60 days after date of publication in the Federal Register*], and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I.C. of the **SUPPLEMENTARY INFORMATION**).

ADDRESSES: The docket for this action, identified by docket identification (ID) number EPA-HQ-OPP-2012-0131, is available at <http://www.regulations.gov> or at the Office of Pesticide Programs Regulatory Public Docket (OPP Docket) in the Environmental Protection Agency Docket Center (EPA/DC), EPA West Bldg., Rm. 3334, 1301 Constitution Ave., NW., Washington, DC 20460-0001. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the OPP Docket is (703) 305-5805. Please review the visitor instructions and additional information about the docket available at <http://www.epa.gov/dockets>.

FOR FURTHER INFORMATION CONTACT: Roger Chesser, Registration Division (7505P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (703) 347-8516; email address: chesser.roger@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document applies to them. Potentially affected entities may include:

- Crop production (NAICS code 111).
- Animal production (NAICS code 112).

- Food manufacturing (NAICS code 311).
- Pesticide manufacturing (NAICS code 32532).

B. How Can I Get Electronic Access to Other Related Information?

You may access a frequently updated electronic version of 40 CFR part 180 through the Government Printing Office's e-CFR site at http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?&c=ecfr&tpl=/ecfrbrowse/Title40/40tab_02.tpl.

C. How Can I File an Objection or Hearing Request?

Under FFDCA section 408(g), 21 U.S.C. 346a, any person may file an objection to any aspect of this regulation and may also request a hearing on those objections. You must file your objection or request a hearing on this regulation in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2012-0131 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing, and must be received by the Hearing Clerk on or before *[insert date 60 days after date of publication in the **Federal Register**]*. Addresses for mail and hand delivery of objections and hearing requests are provided in 40 CFR 178.25(b).

In addition to filing an objection or hearing request with the Hearing Clerk as described in 40 CFR part 178, please submit a copy of the filing (excluding any CBI) for inclusion in the public docket. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit the non-CBI copy

of your objection or hearing request, identified by docket ID number EPA-HQ-OPP-2012-0131, by one of the following methods:

- *Federal eRulemaking Portal*: <http://www.regulations.gov>. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute.

- *Mail*: OPP Docket, Environmental Protection Agency Docket Center (EPA/DC), (28221T), 1200 Pennsylvania Ave., NW. Washington, DC 20460-0001.

- *Hand Delivery*: To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at <http://www.epa.gov/dockets/contacts.htm>.

Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at <http://www.epa.gov/dockets>.

II. Petition for Exemption

In the **Federal Register** of May 2, 2012 (77 FR 25957) (FRL-9346-1), EPA issued a notice pursuant to FFDCA section 408, 21 U.S.C. 346a, announcing the filing of a pesticide petition (PP 1E7900) by ISK Biosciences Corporation, 7470 Auburn Road, Suite A, Concord, OH 44077. The petition requested that 40 CFR 180.920 be amended by establishing an exemption from the requirement of a tolerance for residues of calcium gluconate (CAS Reg. No. 299-28-5) when used as an inert ingredient (sequestrant) in pesticide formulations applied to growing crops. That notice referenced a summary of the petition prepared by ISK Biosciences Corporation, the petitioner, which is available

in the docket, <http://www.regulations.gov>. There were no comments received in response to the notice of filing.

III. Inert Ingredient Definition

Inert ingredients are all ingredients that are not active ingredients as defined in 40 CFR 153.125 and include, but are not limited to, the following types of ingredients (except when they have a pesticidal efficacy of their own): Solvents such as alcohols and hydrocarbons; surfactants such as polyoxyethylene polymers and fatty acids; carriers such as clay and diatomaceous earth; thickeners such as carrageenan and modified cellulose; wetting, spreading, and dispersing agents; propellants in aerosol dispensers; microencapsulating agents; and emulsifiers. The term “inert” is not intended to imply nontoxicity; the ingredient may or may not be chemically active. Generally, EPA has exempted inert ingredients from the requirement of a tolerance based on the low toxicity of the individual inert ingredients.

IV. Aggregate Risk Assessment and Determination of Safety

Section 408(c)(2)(A)(i) of FFDCA allows EPA to establish an exemption from the requirement for a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if EPA determines that the tolerance is “safe.” Section 408(b)(2)(A)(ii) of FFDCA defines “safe” to mean that “there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.” This includes exposure through drinking water and in residential settings, but does not include occupational exposure. Section 408(b)(2)(C) of FFDCA requires EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in

establishing a tolerance and to “ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue....”

EPA establishes exemptions from the requirement of a tolerance only in those cases where it can be clearly demonstrated that the risks from aggregate exposure to pesticide chemical residues under reasonably foreseeable circumstances will pose no appreciable risks to human health. In order to determine the risks from aggregate exposure to pesticide inert ingredients, the Agency considers the toxicity of the inert in conjunction with possible exposure to residues of the inert ingredient through food, drinking water, and through other exposures that occur as a result of pesticide use in residential settings. If EPA is able to determine that a finite tolerance is not necessary to ensure that there is a reasonable certainty that no harm will result from aggregate exposure to the inert ingredient, an exemption from the requirement of a tolerance may be established.

Consistent with FFDCA section 408(c)(2)(A), and the factors specified in FFDCA section 408(c)(2)(B), EPA has reviewed the available scientific data and other relevant information in support of this action. EPA has sufficient data to assess the hazards of and to make a determination on aggregate exposure for calcium gluconate including exposure resulting from the exemption established by this action. EPA's assessment of exposures and risks associated with calcium gluconate follows.

A. Toxicological Profile

EPA has evaluated the available toxicity data and considered their validity, completeness, and reliability as well as the relationship of the results of the studies to

human risk. EPA has also considered available information concerning the variability of the sensitivities of major identifiable subgroups of consumers, including infants and children. Specific information on the studies received and the nature of the adverse effects caused by calcium gluconate as well as the no-observed-adverse-effect-level (NOAEL) and the lowest-observed-adverse-effect-level (LOAEL) from the toxicity studies are discussed in this unit.

Calcium gluconate has been evaluated by the Joint Food and Agriculture Organization/ World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) which determined that calcium gluconate was of very low toxicity and allocated an acceptable daily intake (ADI) of "not specified". The JECFA evaluation of calcium gluconate was part of a group--gluconic acid and its inorganic salts, that were assessed together based on the fact that the calcium, magnesium, potassium, and sodium salts of gluconic acid are freely ionizable and that it was appropriate to allocate ADIs on the basis of data on their corresponding anion (gluconic acid) as calcium gluconate dissociates under normal physiologic conditions into gluconic acid. ADI "not specified" is used to refer to a food substance of very low toxicity, which, on the basis of available data (chemical, biochemical, toxicological, and other) and the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background levels in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for reasons stated in individual evaluations, the establishment of an ADI expressed in numerical form is not necessary. Calcium gluconate was added to the CODEX General Standard for Food Additives (GSFA) in 1999.

Toxicological studies considered by JECFA in their evaluation of gluconic acid and its inorganic salts included acute oral toxicity studies in the rat, mouse, rabbit and hamster with LD₅₀ values ranging from >2,000 milligrams/kilogram (mg/kg) to 7,850 mg/kg. Gluconic acid and its inorganic salts have been tested in *in vitro* assays (bacterial reverse mutation assays) which demonstrated that gluconic acid was not mutagenic with or without metabolic activation.

In various subchronic, chronic, reproductive and developmental studies evaluated using gluconic acid and its inorganic salts by JECFA, no observable adverse effects were noted at or above limit dose levels (i.e., > 1,000 mg/kg/day). (JECFA 1999).

B. Toxicological Points of Departure/Levels of Concern

As discussed above, there was no hazard identified in repeat dose toxicity and reproductive/developmental studies with gluconic acid and its inorganic salts at the limit dose of 1,000 mg/kg/day to either parental animals or their offspring. Thus, due to its low potential hazard and lack of a hazard endpoint, the Agency has determined that a quantitative risk assessment using safety factors applied to a point of departure protective of an identified hazard endpoint is not appropriate for calcium gluconate.

Calcium gluconate was not mutagenic in an *in vitro* chromosome aberration test, bacterial gene mutation test. In addition, the available *in vitro* and *in vivo* mutagenicity data with glucuronic acid and its inorganic salts were negative. Based on the available information from the mutation studies, it is not anticipated to be carcinogenic.

C. Exposure Assessment

No hazard endpoint of concern for calcium gluconate was identified for the acute and chronic dietary assessment (food and drinking water), or for the short, intermediate,

and long term residential assessments (via all exposure routes); therefore, acute and chronic dietary and short-, intermediate-, and long-term residential exposure assessments were not performed.

D. Cumulative Effects from Substances with a Common Mechanism of Toxicity

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider “available information” concerning the cumulative effects of a particular pesticide's residues and “other substances that have a common mechanism of toxicity.”

While the toxicity of calcium gluconate is expected to be similar to the other inorganic salts of gluconic acid as well as gluconic acid itself, there are no toxicological endpoints of concern identified for any of these substances. Therefore a cumulative risk assessment was not performed.

For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see EPA's website at <http://www.epa.gov/pesticides/cumulative>.

E. Safety Factor for Infants and Children

Section 408(b)(2)(C) of FFDCA provides that EPA shall apply an additional tenfold (10X) margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database on toxicity and exposure unless EPA determines based on reliable data that a different margin of safety will be safe for infants and children. This additional margin of safety is commonly referred to as the Food Quality Protection Act Safety Factor (FQPA SF). In

applying this provision, EPA either retains the default value of 10X, or uses a different additional safety factor when reliable data available to EPA support the choice of a different factor.

The toxicity database for calcium gluconate identified no hazard endpoint of concern for calcium gluconate and there is no residual uncertainty regarding prenatal and/or postnatal toxicity. No acute or subchronic neurotoxicity studies are available, but there were no clinical signs of neurotoxicity or any systemic toxicity observed in the available database at doses up to 1,000 mg/kg/day. No developmental or reproductive effects were seen in the available studies at doses up to and including 1,000 mg/kg/day.

Based on this information, there is no concern, at this time, for increased sensitivity to infants and children to calcium gluconate when used as an inert ingredient in pesticide formulations applied to growing crops and a safety factor analysis has not been used to assess risk. For the same reason, EPA has determined that an additional safety factor is not needed to protect the safety of infants and children.

F. Aggregate Risks and Determination of Safety

Given the lack of concern for hazard posed by calcium gluconate, EPA concludes that there are no dietary or aggregate dietary/non-dietary risks of concern as a result of exposure to calcium gluconate in food and water, or from residential exposure. Residues of concern are not anticipated for dietary exposure (food and drinking water) or for residential exposure from the use of calcium gluconate as an inert ingredient in pesticide products. As discussed in this unit, EPA expects aggregate exposure to calcium gluconate to pose no appreciable dietary risk given that the data show a lack of any

systemic toxicity or adverse developmental/reproductive effects at doses up to 1,000 mg/kg/day.

Taking into consideration all available information on calcium gluconate, EPA has determined that there is a reasonable certainty that no harm to any population subgroup, including infants and children, will result from aggregate exposure to calcium gluconate under reasonable foreseeable circumstances. Therefore, the establishment of an exemption from tolerance under 40 CFR 180.920 for residues of calcium gluconate (CAS Reg. No. 299-28-5) when used as an inert ingredient in pesticide formulations applied to growing crops, is safe under FFDCA section 408.

V. Other Considerations

A. Analytical Enforcement Methodology

An analytical method is not required for enforcement purposes since the Agency is establishing an exemption from the requirement of a tolerance without any numerical limitation.

B. International Residue Limits

In making its tolerance decisions, EPA seeks to harmonize U.S. tolerances with international standards whenever possible, consistent with U.S. food safety standards and agricultural practices. EPA considers the international maximum residue limits (MRLs) established by the Codex Alimentarius Commission (Codex), as required by FFDCA section 408(b)(4). The Codex Alimentarius is a joint United Nations Food and Agriculture Organization/World Health Organization food standards program, and it is recognized as an international food safety standards-setting organization in trade agreements to which the United States is a party. EPA may establish a tolerance that is

different from a Codex MRL; however, FFDCA section 408(b)(4) requires that EPA explain the reasons for departing from the Codex level. The CODEX has not established a MRL for calcium gluconate.

VI. Conclusions

Therefore, an exemption from the requirement of a tolerance is established under 40 CFR 180.920 for calcium gluconate (CAS Reg. No. 299-28-5) when used as an inert ingredient (sequestrant) in pesticide formulations applied to growing crops.

VII. Statutory and Executive Order Reviews

This final rule establishes an exemption from the requirement of a tolerance under FFDCA section 408(d) in response to a petition submitted to the Agency. The Office of Management and Budget (OMB) has exempted these types of actions from review under Executive Order 12866, entitled “Regulatory Planning and Review” (58 FR 51735, October 4, 1993). Because this final rule has been exempted from review under Executive Order 12866, this final rule is not subject to Executive Order 13211, entitled “Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use” (66 FR 28355, May 22, 2001) or Executive Order 13045, entitled “Protection of Children from Environmental Health Risks and Safety Risks” (62 FR 19885, April 23, 1997). This final rule does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA) (44 U.S.C. 3501 *et seq.*), nor does it require any special considerations under Executive Order 12898, entitled “Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations” (59 FR 7629, February 16, 1994).

Since tolerances and exemptions that are established on the basis of a petition under FFDCA section 408(d), such as the tolerance exemption in this final rule, do not require the issuance of a proposed rule, the requirements of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*), do not apply.

This final rule directly regulates growers, food processors, food handlers, and food retailers, not States or tribes, nor does this action alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of FFDCA section 408(n)(4). As such, the Agency has determined that this action will not have a substantial direct effect on States or tribal governments, on the relationship between the national government and the States or tribal governments, or on the distribution of power and responsibilities among the various levels of government or between the Federal Government and Indian tribes. Thus, the Agency has determined that Executive Order 13132, entitled “Federalism” (64 FR 43255, August 10, 1999) and Executive Order 13175, entitled “Consultation and Coordination with Indian Tribal Governments” (65 FR 67249, November 9, 2000) do not apply to this final rule. In addition, this final rule does not impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act of 1995 (UMRA) (2 U.S.C. 1501 *et seq.*).

This action does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA) (15 U.S.C. 272 note).

VIII. Congressional Review Act

Pursuant to the Congressional Review Act (5 U.S.C. 801 *et seq.*), EPA will

submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of the rule in the **Federal Register**. This action is not a “major rule” as defined by 5 U.S.C. 804(2).

List of Subjects in 40 CFR Part 180

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: October 15, 2012.

Lois Rossi,

Director, Registration Division, Office of Pesticide Programs.

Therefore, 40 CFR chapter I is amended as follows:

PART 180—[AMENDED]

1. The authority citation for part 180 continues to read as follows:

Authority: 21 U.S.C. 321(q), 346a and 371.

2. In §180.920, the table is amended by adding alphabetically the following entry immediately before the entry for “Camphor (CAS Reg. No. 76-22-2).”

§ 180.920 Inert ingredients used pre-harvest; exemptions from the requirement of a tolerance.

* * * * *

Inert ingredients	Limits	Uses
* * * *	*	* *
Calcium gluconate (CAS Reg. No. 299-28-5)	Sequestrant
* * * *	*	* *

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